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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,627	04/14/2004	Renata Pasqualini	UTSC:858US	6275

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,627	PASQUALINI ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,9-23 and 25-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-7,9-23,25-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt is acknowledged of an amendment filed 1/9/06. Claims 1, 8, 24, and 39 were canceled. Claims 2, 11, 13-15, 17, 19, 20, 22, 23, and 25 were amended. Presently claims 2-7, 9-23, and 25-38 are pending and under examination. Any rejection not addressed hereinbelow has been withdrawn.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

3. Claims 2-7, 9-17, 19-23, and 25-38 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow (Antibodies: A Laboratory Manual (1988), of record) in view of Jat (Proc Natl Acad Sci USA 88: 5096-5100 (1991), of record), Kano (JP62195296, of record) and Kanki (Hybridoma 13: 327-330 (1994), of record). The claims are drawn to a method of producing an antibody-producing cell with a conditional oncogene which can be a temperature sensitive SV40 large T antigen (TAg), which can be the A58S mutant allele of TAg, where the cells are produced at between 25°C and 35°C, ideally at 33°C.

4. Harlow teaches all of the standard procedures for immunizing mice, isolating the spleen cells, culturing the cells, assessing the antibody production after immortalization, producing monoclonal antibodies through limiting dilution, and producing polyclonal antibodies in the absence of single cell cloning. Harlow does not teach immortalization of the antibody-producing cells in the absence of hybridoma formation with no mention of temperature sensitive TAg.

5. Jat teaches a transgenic mouse comprising the A58S SV40 TAg allele providing conditionally immortal cells. In order to derive these immortal cell lines the permissive temperature for growth is 33°C. Jat teaches that immortalized skin fibroblasts and thymic stromal cells are successfully produced from these mice (Abstract and page5097, column1, sixth full paragraph, and page 5099, column 1, first full paragraph). Indeed Jat asserts that "the use of fibroblast populations can be transferred readily to other cell systems" (page 5096, second column).

6. One would have been motivated to use the transgenic mice of Jat in the antibody production protocols of Harlow because the establishment of immortalized cell lines from the mouse of Jat is a simple procedure of culturing the cells at the permissive temperature. The skilled artisan would have reasonably expected the mice of Jat to lead to the production of stable antibody-producing cells in the absence of hybridoma formation because Kano had taught that an oncogene, i.e. SV40 DNA could indeed lead to the immortalization of a stable antibody-producing cell, and Kanki had taught that the SV40 early region, which comprises TAg, could indeed immortalize B cells. Therefore, it would have been obvious to one of ordinary skill in the art to produce antibodies and antibody-producing cells in the mice of Jat in order to form antibody-producing cells in the absence of hybridoma formation.

Response to Arguments

7. Applicant's arguments filed 1/9/06 have been fully considered but they are not persuasive. Applicant states "that Harlow *specifically teaches* that hybridoma formation is *an absolute requirement* for the production of monoclonal antibodies" (page 15, first paragraph of

the amendment). First nowhere in the cited quotation of Harlow is any such requirement made by Harlow. Further Applicant has not pointed to where Harlow makes this statement. To counter this, Kumar (Immunol Lett 65: 153-159 (1999), of record) clearly states, "Nonetheless, direct immortalization of B cells using the oncogenes described in this article provides and alternative approach to generate monoclonal antibodies" (page 159, last line of Conclusion).

8. Applicant next argues that one would not have been motivated to employ any alternative approach aside form production of monoclonal antibodies by standard mean as there is no evidence of a problem to be solved. It is unclear why Applicant would hold this position as the numerous articles cited in the Office Action mailed 10/6/05 all teach of different ways of immortalizing B cells in the absence of hybridoma formation (see Kano, Kumar, Kanki, Kempkes (Proc Natl Acad Sci USA 92: 5875-5879 (1995), of record), and Gorny (Proc Natl Acad Sci USA 86: 1624-1628 (1989), of record). Specifically, the instantly claimed methods appear to simply be a variation on the methods taught by Kano, who clearly states that SV40, i.e. comprising TAg, is used to create monoclonal antibodies in the absence of cell fusion (see the whole Abstract). If indeed it was the view of the skilled artisan that hybridoma formation was the perfect method for monoclonal antibody production, why then would so many groups, over an essentially 15-20 year period of time, all apparently seek to immortalized B cells in the absence of hybridoma formation? Indeed the passage of Harlow quoted at the bottom of page 14 of the amendment, clearly identifies problems with using hybridomas for monoclonal antibody production: "Hybridomas production seldom takes less than 2 months from start to finish, and it can take well over a year...Any one of these stages may proceed very quickly, but all have inherent problems that should be considered prior to the start of the project". Thus it seem clear

that Harlow recognized problems with the use of hybridomas for monoclonal antibody formation and production and indeed many of skill in the art recognized these problems and made efforts to circumvent the need for hybridoma production (see particularly Kumar and Kano). Indeed the mice of Jat simply provide a straightforward method to produce antibodies in the absence of hybridoma formation.

9. Claim 18 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow, Jat, Kano, and Kanki as applied to claims 2-7, 9-17, 19-23, and 25-38 above, and further in view of Green (J Immunol Meth 231: 11-23 (1999), of record).

10. Harlow, Jat, Kano, and Kanki teach each of the limitations as described above, but do not teach the use of a mouse comprising the genetic complement for producing human antibodies.

11. Green teaches the XENOMOUSE which allows for the production of human monoclonal antibodies from a mouse. The skilled artisan would have readily recognized the need to interbreed the XENOMOUSE to the mouse of Jat in order to produce a mouse that could produce human antibodies, and produce immortalized B cell clones in the absence of hybridoma formation. One would have been motivated to use the mouse as taught by Green for the production of antibodies as taught in combination by Harlow, Jat, Kano, and Kanki because: "The utility of the XENOMOUSE strains for the generation of large panels of high-affinity, fully human mAbs can be made available to researchers in the academic and private sectors, and should accelerate the development and application of mAbs as therapeutics for human disease" (Green, last line of abstract). Therefore, it would have been obvious to one of ordinary skill in the art to use a mouse transgenic both in the production of human antibodies, and transgenic for

the temperature sensitive allele of TAg in order to produce antigen-specific B cells, through the combined teachings of Harlow, Jat, Green, Kano, and Kanki.

Response to Arguments

12. Applicant's arguments filed 1/9/06 have been fully considered but they are not persuasive. Applicant essentially argues that Green does not overcome the alleged deficiencies of Harlow, Jat, Kano, and Kanki). These arguments were addressed above and were not found to be persuasive.

13. Thus, considering the totality of arguments presented, it is clear that claimed invention would indeed have been obvious to one of ordinary skill in the art.

Conclusion

14. No claim is allowed.

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER